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Spina Bifida and Cleft Lip among Newborns of Norwegian Women with Epilepsy: Changes Related to the Use of Anticonvulsants

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ABSTRACT

Objectives. This study examined the connection between the use of anticonvulsants for epilepsy during or before pregnancy and the risk of spina bifida and cleft lip in newborns.

Methods. Among mothers registered from 1967 to 1992 by the Medical Birth Registry of Norway, 7588 who had epilepsy were identified and their newborns' prevalence of spina bifida and cleft lip examined.

Results. The odds ratio of spina bifida in children of mothers with epilepsy compared with other children increased from 1.5 in 1967 through 1980 (95% confidence interval [CI] = 0.3, 4.5) to 4.4 in 1981 through 1992 (95% CI = 2.0, 8.5). The odds ratio of cleft lip, however, decreased from 3.0 before 1981 (95% CI = 1.6, 5.1) to 1.1 after 1981 (95% CI = 0.4, 2.3).

Conclusions. This shift toward more serious birth defects is consistent with the different teratogenic effects of newer and older anticonvulsants. (*Am J Public Health.* 1996;86:1454–1456)

Introduction

Anticonvulsants have, for a long time, been suspected teratogens, with respect to both minor and major malformations.[1–6] For valproic acid, an association with spina bifida was already suspected in 1982.[2] Since then, several studies have supported a causal relationship.[5] The risk of spina bifida among valproic acid–exposed infants has been estimated to be about 2%, compared with 0.05% among unexposed infants. An increased risk of spina bifida is also suspected after use of carbamazepine, but the risk is estimated to be less than 1%.[5] Orofacial clefts have been associated with the use of phenytoin and phenobarbital.[6] We hypothesized that secular changes in the use of anticonvulsants could be reflected in the occurrence of spina bifida and orofacial clefts among children of mothers with epilepsy.

Methods

The Medical Birth Registry of Norway was established in 1967 and is a population-based compulsory notification system covering all births in Norway. The registry holds information about mothers' health before and during the pregnancy, about the delivery, and about the child. Spina bifida and orofacial clefts are reported with a certainty of more than 80%[7] and are probably the most precisely ascertained types of defects in the registry. Furthermore, it is not likely that ascertainment is much affected either by time or by epilepsy status. Secular trends in the occurrence of these defects may therefore be studied without serious ascertainment bias.

From 1967 through 1992, 1 506 851 newborns were identified. All together, 7558 children had mothers with a recorded history of epilepsy either before or during the pregnancy. Mothers without epilepsy were used as a control group. Since valproic acid was in regular use after 1980, the data were divided into one period from 1967 through 1980 and a second period from 1981 through 1992. This categorization was decided upon before the data were analyzed.

With the use of odds ratios, the prevalences of spina bifida and orofacial clefts in newborns with mothers who had epilepsy were compared with those observed in newborns of mothers without epilepsy. Risks of birth defects are small, and thus, odds ratios can provide a good approximation of relative risks. Secular changes in odds ratios of birth defects were studied by exact logistic models

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with the use of the computer program LogXact.[8] All confidence intervals given are exact 95% confidence intervals of odds ratios. *P* values refer to two-sided tests.

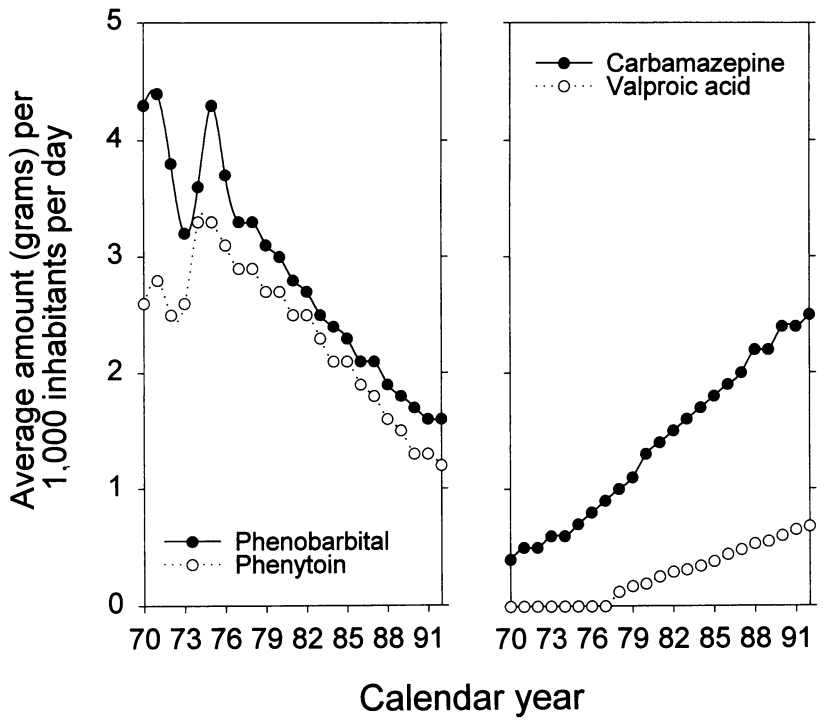
Results

Data on drug use in the Norwegian population were obtained from the Norwegian Medicinal Depot. There has been a substantial decrease in the use of phenobarbital and phenytoin since 1970. In contrast, the use of carbamazepine increased throughout the study period, and the use of valproic acid has increased since its introduction in Norway in 1977 (Figure 1).

As Table 1 shows, among the children of mothers with epilepsy, we observed 12 cases of spina bifida, 3 cases (8.2 per 10 000) in the first period (1967 through 1980) and 9 cases (23.1 per 10 000) in the second period (1981 through 1992). The prevalence of spina bifida in the control group was 5 per 10 000 births in both the first and the second period. The odds ratios for the two periods were 1.5 (95% confidence interval [CI] = 0.3, 4.5) and 4.4 (95% CI = 2.0, 8.5), respectively. However, these odds ratios were not significantly different ($P = .17$). Still, the data indicate a threefold increase in risk over time that a mother with epilepsy will have an infant with spina bifida, and the risk was significantly different from that for the control group only in the most recent period.

Likewise, 20 cases of cleft lip with or without cleft palate were observed, 14 cases (38.3 per 10 000) in the first period and 6 cases (15.4 per 10 000) in the second period (Table 1). In the control group, the prevalence of cleft lip was 12.8 in the first period and 14.4 in the last. The odds ratios between infants of mothers with and without epilepsy for the two periods were 3.0 (95% CI = 1.6, 5.1) and 1.1 (95% CI = 0.4, 2.3), respectively. This drop in odds ratio was significant ($P = .047$). For isolated cleft palate, the odds ratios were 1.9 and 2.8 for the first and the second period and were not significantly different ($P = .8$).

Among children of mothers with epilepsy, the odds ratio of spina bifida between the second and the first time period was 2.8. The odds ratio of cleft lip between the second and the first time period was 0.4. These odds ratios were significantly different ($P = .03$). Thus, the trends in risks for the two types of defects among children of mothers with epilepsy were different.



Source. Data are from the Norwegian Medicinal Depot.

FIGURE 1—The average amount used, per 1000 inhabitants per day, of phenobarbital and phenytoin and of carbamazepine and valproic acid in Norway, from 1970 to 1992.

TABLE 1—The Occurrence of Spina Bifida and Cleft Lip in Children of Mothers with and without Epilepsy, by Year of Birth, Medical Birth Registry of Norway, 1967 through 1992

Year of Birth	Maternal Epilepsy	Cases		Total No. Newborns
		Spina Bifida	Cleft Lip[a]	
1967–1980	Yes	3	14	3 659
	No	449	1071	839 653
	OR (95% CI)	1.5 (0.3, 4.5)	3.0 (1.6, 5.1)	. . .
1981–1992	Yes	9	6	3 899
	No	344	953	659 640
	OR (95% CI)	4.4 (2.0, 8.5)	1.1 (0.4, 2.3)	. . .

Note. OR = odds ratio; CI = confidence interval.
[a]Cleft lip with or without cleft palate.

Discussion

The teratogenic effects of the drugs valproic acid and phenytoin/phenobarbital best explain the similar secular trends in their use and the occurrence of spina bifida and orofacial cleft among the potentially drug-exposed children. Still more important, possible attempts at risk reduction—such as using effective contraception when these drugs are taken or replacing the drug when a pregnancy is detected—have not eliminated the excess risk among mothers with epilepsy.

Complete information about individual medication is not available in the Medical Birth Registry of Norway. Be-

cause some anticonvulsants are teratogens, a change in treatment may occur when a patient is known to be pregnant. Thus, the level of exposure to the infant will in any case be difficult to evaluate.

Treating physicians must be informed about the teratogenic effects of these drugs, and they should advise women of reproductive age who use valproic acid, or other suspected teratogenic anticonvulsants, to use effective contraception if they do not wish to become pregnant. Women with epilepsy did have fewer children than other women throughout the period. About 50% of births among women with epilepsy were first births, compared with about 40% among other women.

Folic acid supplementation has been suggested for patients using phenytoin or phenobarbital,[9] and this is used as a preventive measure in groups at high risk of spina bifida.[10] Folic acid should therefore be considered as a routine supplement to all anticonvulsants for fertile women.

In conclusion, this study is a strong confirmation of the different teratogenic effects of newer drugs like valproic acid and carbamazepine and older drugs like phenytoin and phenobarbital. The changes we observed indicate that the increased risk of birth defects among children of mothers with epilepsy is entirely an effect of epilepsy therapy, not an effect of maternal epilepsy. □

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Lower Respiratory Tract Infections among Norwegian Infants with Siblings in Day Care

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ABSTRACT

Objectives. The purpose of this study was to assess the role of siblings in day care as a determinant of infants' risk of lower respiratory tract infections.

Methods. A total of 3238 children (86%) out of 3754 Oslo, Norway, newborns recruited in 1992/93 were followed for 1 year.

Results. In logistic regression analysis, the risk of infection was increased in (1) infants with one or more siblings compared with infants without siblings (adjusted odds ratio [OR] = 2.3; 95% confidence interval [CI] = 1.84, 2.85) and (2) infants with one or more siblings in day care compared with infants with siblings not in day care (adjusted OR = 1.7; 95% CI = 1.21, 2.26).

Conclusions. The results suggest that siblings in day care outside the home increase infants' risk of lower respiratory tract infections. (*Am J Public Health.* 1996;86:1456–1459)

Introduction

Respiratory tract infections are major causes of morbidity among small children.[1–6] Such infections in early life have been suggested to predispose children to later obstructive airway diseases and reduced lung function.[7–9] Previous studies have shown that children with siblings[3,10–13] and children attending day care outside the home[11,14–16] have more respiratory illnesses than those without siblings and those who do not attend day care.

The objective of the present study was to assess further the role of siblings as a determinant of an infant's risk for lower respiratory tract infections. In Norway, because of a long maternity leave policy, only a few children attend day care outside the home before the end of their first year. Yet older siblings are commonly in day care outside the home. This situation has made it possible to study whether siblings in day care increase the risk of lower respiratory tract infections in infants staying at home.

Methods

Study Population and Data Collection

Families of all infants born at the two main birth clinics in Oslo during a period of 15 months from 1992 to 1993 were considered for this study (n = 6400). The families had to meet the following criteria: a permanent address within the city of Oslo, no plans of moving from Oslo within the near future, infant birthweight greater than 2000 g, no serious illness in infant

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